44. (amended) A method of preventing or delaying the onset of an increase in insulin levels in an animal comprising administering to said animal an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human PI3K p85 of SEQ ID NO: 1, wherein said compound specifically hybridizes with and inhibits the expression of human PI3K p85.

REMARKS

Claims 1, 2 and 4-63 are pending in the instant application. Claims 1, 2 and 4-63 have been rejected. Claims 1, 2, 4-23, 32-39 and 48-63 have been canceled. Claims 24, 28, 40 and 44 have been amended to make the dependent claims independent claims. No new matter has been added by these amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Election/Restriction

The Examiner has deemed proper and made final the Restriction Requirement for the instant invention. Applicants acknowledge the Examiner's response to Applicants' traversal.

II. Double Patenting

Claims 1, 2, 4-14 and 23 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,100,090. Applicants have canceled claim 1, 2, 4-14 and 23 making this rejection moot. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claim 48 has been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 48 has been canceled making this rejection moot. Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 23 and 49-57 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed

invention. Claims 23 and 49-57 have been canceled without prejudice. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 15-62 have been rejected under 35 U.S.C. 112, first paragraph, because the specification as filed does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner acknowledges that the specification is enabling for compositions and methods for inhibiting expression of human PI3K p85 of SEQ ID NO: 1 *in vitro*. However, the Examiner suggests that the specification does not reasonably provide enablement for antisense oligonucleotides as claimed that target and inhibit expression of a nucleic acid encoding a truncated form of human PI3K p85 of SEQ ID NO: 1 or any other splice variants of this gene, or for antisense compounds that alter the ratio of splice variants of this gene, or for treatment or prevention of any disease or condition associated with PI3K p85 expression in an organism, or for modulation of signal transduction in an organism through administration of the claimed antisense compounds. The Examiner cites articles on the technology of antisense to support this position. Applicants respectfully traverse this rejection.

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Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to several articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells and *in vivo* in animals in the instant invention would also occur *in vivo* in animals that would include humans.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological

distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos in vivo but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in the instant specification, are directly applicable to predicting in vivo activity. Further, the specification as filed provides in vivo data using antisense compounds of the instant invention to alter physiology, a pharmacological effect. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been

reported in which antisense activity was conclusively demonstrated [in vitro]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and then studies in humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* and *in vivo* pharmacological studies would not be predictive of activity *in vivo* in humans.

Moreover, the paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Pal et al. (1999) is a review paper on the technology of gene therapy, not antisense. Gene therapy is an entirely different technology with its own set of issues for drug development. Citing this paper to support the unpredictability of

antisense is inappropriate. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Agrawal and Kandimalla (2000) is another review paper on the technology of antisense. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Chirila et al. (2002) is a review of the use of polymers for delivery of antisense compounds. Although this paper reviews problems that have arisen during development of antisense, problems that are addressed and solved in the specification as filed, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Tamm et al. (2001) is a review paper on the use of antisense compounds to treat cancer. The paper discusses the strides that have been made in cancer treatment and the potential for use of antisense compounds, including a discussion of the use of these compounds in clinical studies. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

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Finally, the press release cited by the Examiner does not support the conclusion that data from *in vitro* studies in cells and *in vivo* studies in animals is not predictive of *in vivo* activity in humans. This failure of a clinical trial for Crohn's disease is a very different standard where a drug must be statistically significantly better than a placebo on a particular endpoint. It does not mean the drug was without activity to inhibit gene expression when results from pre-clinical *in vitro* and *in vivo* studies are extrapolated to predict *in vivo* activity in humans.

In an earnest effort to advance the prosecution of this case, Applicants have canceled claims 15-23, 32-39 and 48-63 without prejudice, claims that are directed to use of antisense targeted to truncated forms of PI3K p85 as well as method of treatment claims for specific diseases and modulation of signal transduction. Applicants respectfully point out that the remaining claims, 24-31 and 40-47, recite methods for decreasing blood glucose levels in animals, methods for decreasing insulin levels in animals, and methods of preventing or delaying onset of increases in blood glucose or insulin in animals. Each of these claims is support by the teachings in the specification as filed (see pages 95 and 99) where it is shown *in vivo* in animals that antisense of the instant

invention is capable of reducing blood glucose levels without producing hypoglycemia in animals, as well as reducing insulin levels in animals, results that are consistent with the scope of claims 24-31 and 40-47. It is commonly understood that results of well-designed pharmacological studies *in vivo* in animals are predictive of production of the same effects in humans, especially when the endpoint being measured is one which is known to occur in both animals tested and humans. An even cursory review of the published scientific literature reveals that rodents are used routinely as models for blood glucose and insulin responses in humans. Accordingly, the specification as filed meets the requirements of 35 U.S.C. 112, first paragraph with respect to the pending claims 24-31 and 40-47. Withdrawal of this rejection is therefore respectfully requested.

V. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2 and 12-15 have been rejected under 35 U.S.C. 102(b) as being anticipated by either Zauli et al. (1994) or Skorski et al. (1995). The Examiner suggests that either of those papers teach inhibition of human p21^{ras} in cells and tissues in culture using antisense compounds as claimed. Claims 1, 2 and 12-

15 have been canceled without prejudice. Withdrawal of this rejection is therefore respectfully requested.

VI. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Skorski et al. and Zauli et al., and further in view of Schlessinger et al. (WO 92/13001), the combination in view of Milner et al. (1997) and Baracchini et al. (US Patent 5,801,154). As discussed supra, claims 1, 2 and 4-14 have been canceled without prejudice making this rejection moot. Withdrawal of this rejection is therefore respectfully requested.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

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Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: February 19, 2003

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 2, 4-23, 32-39 and 48-63 have been canceled without prejudice.

Claims 20, 28, 40 and 44 have been amended as follows:

24. (amended) A method of decreasing blood glucose levels in an animal comprising administering to said animal ~~the antisense compound of claim 1~~ an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule of SEQ ID NO: 1 encoding human PI3K p85, wherein said compound specifically hybridizes with and inhibits the expression of human PI3K p85.

28. (amended) A method of decreasing insulin levels in an animal comprising administering to said animal ~~the antisense compound of claim 1~~ an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human PI3K p85 of SEQ ID NO: 1, wherein said compound specifically hybridizes with and inhibits the expression of human PI3K p85.

40. (amended) A method of preventing or delaying the onset of an increase in blood glucose levels in an animal comprising

administering to said animal ~~the antisense compound of claim 1~~ an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human PI3K p85 of SEQ ID NO: 1, wherein said compound specifically hybridizes with and inhibits the expression of human PI3K p85.

44. (amended) A method of preventing or delaying the onset of an increase in insulin levels in an animal comprising administering to said animal ~~the antisense compound of claim 1~~ an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding human PI3K p85 of SEQ ID NO: 1, wherein said compound specifically hybridizes with and inhibits the expression of human PI3K p85.